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(54) Title: PAPILLOMA VIRUS CAPSOMERE VACCINE FORMULATIONS AND METHODS OF USE

(57) Abstract

Vaccine formulations comprising viral capsomeres are disclosed along with methods for their production. Therapeutic and prophylactic methods of use for the vaccine formulations are also disclosed.

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PAPILLOMA VIRUS CAPSOMERE VACCINE FORMULATIONS AND METHODS OF USE

FIELD OF THE INVENTION

The present invention relates to vaccine formulations comprising papilloma virus proteins, either as fusion proteins, truncated proteins, or truncated fusion proteins. The invention further embraces methods for producing capsomeres of the formulations, as well as prophylactic and therapeutic methods for their use.

BACKGROUND

Infections with certain high-risk strains of genital papilloma viruses in humans (HPV) -- for example, HPV 16, 18, or 45 -- are believed to be the main risk factor for the formation of malignant tumors of the anogenital tract. Of the possible malignancies, cervical carcinoma is by far the most frequent; according to an estimate by the World Health Organization (WHO), almost 500,000 new cases of the disease occur annually. Because of the frequency with which this pathology occurs, the connection between HPV infection and cervical carcinoma has been extensively examined, leading to numerous generalizations.

For example, precursor lesions of cervical intraepithelial neoplasia (CIN) are known to be caused by papilloma virus infections [Crum, *New Eng. J. Med. 310*:880-883 (1984)]. DNA from the genomes of certain HPV types, including for example, strains 16, 18, 33, 35, and 45, have been detected in more than 95% of tumor biopsies from patients with this disorder, as well as in primary cell lines cultured from the tumors. Approximately 50 to 70% of the biopsied CIN tumor cells have been found to include DNA derived only from HPV 16.

The protein products of the HPV 16 and HPV 18 early genes E6 and E7 have been detected in cervical carcinoma cell lines as well as in

by BPV VLPs. The mouse sera was therefore positive for neutralizing antibodies against the human VLPs and this differential neutralization was most likely the result of antibody specificity for epitopes against which the antibodies were raised.

Numerous modifications and variations in the invention as set forth in the above illustrative examples are expected to occur to those skilled in the art. Consequently only such limitations as appear in the appended claims should be placed on the invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(ii) TITLE OF INVENTION: Papilloma Virus Capsomere Vaccine Formulations and Methods of Use

(iii) NUMBER OF SEQUENCES: 27

(iv) CORRESPONDENCE ADDRESS:
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(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Williams Jr., Joseph A.
(B) REGISTRATION NUMBER: 38,659
(C) REFERENCE/DOCKET NUMBER: 27013/34028

(ix) TELECOMMUNICATION INFORMATION:
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(B) TELEFAX: 312-474-0448

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1518 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1518

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
ATG TCT CTT TGG CTG CCT AGT GAG GCC ACT GTC TAC TTG CCT CCT GTC        48
Met Ser Leu Trp Leu Pro Ser Glu Ala Thr Val Tyr Leu Pro Pro Val
 1               5                  10                  15

CCA GTA TCT AAG GTT GTA AGC ACG GAT GAA TAT GTT GCA CGC ACA AAC        96
Pro Val Ser Lys Val Val Ser Thr Asp Glu Tyr Val Ala Arg Thr Asn
            20                  25                  30
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ATA TAT TAT CAT GCA GGA ACA TCC AGA CTA CTT GCA GTT GGA CAT CCC      144
Ile Tyr Tyr His Ala Gly Thr Ser Arg Leu Leu Ala Val Gly His Pro
         35                  40                  45

TAT TTT CCT ATT AAA AAA CCT AAC AAT AAC AAA ATA TTA GTT CCT AAA      192
Tyr Phe Pro Ile Lys Lys Pro Asn Asn Asn Lys Ile Leu Val Pro Lys
     50                  55                  60

GTA TCA GGA TTA CAA TAC AGG GTA TTT AGA ATA CAT TTA CCT GAC CCC      240
Val Ser Gly Leu Gln Tyr Arg Val Phe Arg Ile His Leu Pro Asp Pro
 65                  70                  75                  80

AAT AAG TTT GGT TTT CCT GAC ACC TCA TTT TAT AAT CCA GAT ACA CAG      288
Asn Lys Phe Gly Phe Pro Asp Thr Ser Phe Tyr Asn Pro Asp Thr Gln
                 85                  90                  95

CGG CTG GTT TGG GCC TGT GTA GGT GTT GAG GTA GGT CGT GGT CAG CCA      336
Arg Leu Val Trp Ala Cys Val Gly Val Glu Val Gly Arg Gly Gln Pro
            100                 105                 110

TTA GGT GTG GGC ATT AGT GGC CAT CCT TTA TTA AAT AAA TTG GAT GAC      384
Leu Gly Val Gly Ile Ser Gly His Pro Leu Leu Asn Lys Leu Asp Asp
        115                 120                 125

ACA GAA AAT GCT AGT GCT TAT GCA GCA AAT GCA GGT GTG GAT AAT AGA      432
Thr Glu Asn Ala Ser Ala Tyr Ala Ala Asn Ala Gly Val Asp Asn Arg
    130                 135                 140

GAA TGT ATA TCT ATG GAT TAC AAA CAA ACA CAA TTG TGT TTA ATT GGT      480
Glu Cys Ile Ser Met Asp Tyr Lys Gln Thr Gln Leu Cys Leu Ile Gly
145                 150                 155                 160

TGC AAA CCA CCT ATA GGG GAA CAC TGG GGC AAA GGA TCC CCA TGT ACC      528
Cys Lys Pro Pro Ile Gly Glu His Trp Gly Lys Gly Ser Pro Cys Thr
                165                 170                 175

AAT GTT GCA GTA AAT CCA GGT GAT TGT CCA CCA TTA GAG TTA ATA AAC      576
Asn Val Ala Val Asn Pro Gly Asp Cys Pro Pro Leu Glu Leu Ile Asn
            180                 185                 190

ACA GTT ATT CAG GAT GGT GAT ATG GTT GAT ACT GGC TTT GGT GCT ATG      624
Thr Val Ile Gln Asp Gly Asp Met Val Asp Thr Gly Phe Gly Ala Met
        195                 200                 205

GAC TTT ACT ACA TTA CAG GCT AAC AAA AGT GAA GTT CCA CTG GAT ATT      672
Asp Phe Thr Thr Leu Gln Ala Asn Lys Ser Glu Val Pro Leu Asp Ile
    210                 215                 220

TGT ACA TCT ATT TGC AAA TAT CCA GAT TAT ATT AAA ATG GTG TCA GAA      720
Cys Thr Ser Ile Cys Lys Tyr Pro Asp Tyr Ile Lys Met Val Ser Glu
225                 230                 235                 240

CCA TAT GGC GAC AGC TTA TTT TTT TAT TTA CGA AGG GAA CAA ATG TTT      768
Pro Tyr Gly Asp Ser Leu Phe Phe Tyr Leu Arg Arg Glu Gln Met Phe
                245                 250                 255

GTT AGA CAT TTA TTT AAT AGG GCT GGT GCT GTT GGT GAA AAT GTA CCA      816
Val Arg His Leu Phe Asn Arg Ala Gly Ala Val Gly Glu Asn Val Pro
            260                 265                 270

GAC GAT TTA TAC ATT AAA GGC TCT GGG TCT ACT GCA AAT TTA GCC AGT      864
Asp Asp Leu Tyr Ile Lys Gly Ser Gly Ser Thr Ala Asn Leu Ala Ser
        275                 280                 285
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TCA AAT TAT TTT CCT ACA CCT AGT GGT TCT ATG GTT ACC TCT GAT GCC      912
Ser Asn Tyr Phe Pro Thr Pro Ser Gly Ser Met Val Thr Ser Asp Ala
    290                 295                 300

CAA ATA TTC AAT AAA CCT TAT TGG TTA CAA CGA GCA CAG GGC CAC AAT      960
Gln Ile Phe Asn Lys Pro Tyr Trp Leu Gln Arg Ala Gln Gly His Asn
305                 310                 315                 320

AAT GGC ATT TGT TGG GGT AAC CAA CTA TTT GTT ACT GTT GTT GAT ACT     1008
Asn Gly Ile Cys Trp Gly Asn Gln Leu Phe Val Thr Val Val Asp Thr
                325                 330                 335

ACA CGC AGT ACA AAT ATG TCA TTA TGT GCT GCC ATA TCT ACT TCA GAA     1056
Thr Arg Ser Thr Asn Met Ser Leu Cys Ala Ala Ile Ser Thr Ser Glu
            340                 345                 350

ACT ACA TAT AAA AAT ACT AAC TTT AAG GAG TAC CTA CGA CAT GGG GAG     1104
Thr Thr Tyr Lys Asn Thr Asn Phe Lys Glu Tyr Leu Arg His Gly Glu
        355                 360                 365

GAA TAT GAT TTA CAG TTT ATT TTT CAA CTG TGC AAA ATA ACC TTA ACT     1152
Glu Tyr Asp Leu Gln Phe Ile Phe Gln Leu Cys Lys Ile Thr Leu Thr
    370                 375                 380

GCA GAC GTT ATG ACA TAC ATA CAT TCT ATG AAT TCC ACT ATT TTG GAG     1200
Ala Asp Val Met Thr Tyr Ile His Ser Met Asn Ser Thr Ile Leu Glu
385                 390                 395                 400

GAC TGG AAT TTT GGT CTA CAA CCT CCC CCA GGA GGC ACA CTA GAA GAT     1248
Asp Trp Asn Phe Gly Leu Gln Pro Pro Pro Gly Gly Thr Leu Glu Asp
                405                 410                 415

ACT TAT AGG TTT GTA ACC TCC CAG GCA ATT GCT TGT CAA AAA CAT ACA     1296
Thr Tyr Arg Phe Val Thr Ser Gln Ala Ile Ala Cys Gln Lys His Thr
            420                 425                 430

CCT CCA GCA CCT AAA GAA GAT CCC CTT AAA AAA TAC ACT TTT TGG GAA     1344
Pro Pro Ala Pro Lys Glu Asp Pro Leu Lys Lys Tyr Thr Phe Trp Glu
        435                 440                 445

GTA AAT TTA AAG GAA AAG TTT TCT GCA GAC CTA GAT CAG TTT CCT TTA     1392
Val Asn Leu Lys Glu Lys Phe Ser Ala Asp Leu Asp Gln Phe Pro Leu
    450                 455                 460

GGA CGC AAA TTT TTA CTA CAA GCA GGA TTG AAG GCC AAA CCA AAA TTT     1440
Gly Arg Lys Phe Leu Leu Gln Ala Gly Leu Lys Ala Lys Pro Lys Phe
465                 470                 475                 480

ACA TTA GGA AAA CGA AAA GCT ACA CCC ACC ACC TCA TCT ACC TCT ACA     1488
Thr Leu Gly Lys Arg Lys Ala Thr Pro Thr Thr Ser Ser Thr Ser Thr
                485                 490                 495

ACT GCT AAA CGC AAA AAA CGT AAG CTG TAA                            1518
Thr Ala Lys Arg Lys Lys Arg Lys Leu  *
            500                 505
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 506 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Ser Leu Trp Leu Pro Ser Glu Ala Thr Val Tyr Leu Pro Pro Val
 1               5                  10                  15

Pro Val Ser Lys Val Val Ser Thr Asp Glu Tyr Val Ala Arg Thr Asn
            20                  25                  30

Ile Tyr Tyr His Ala Gly Thr Ser Arg Leu Leu Ala Val Gly His Pro
        35                  40                  45

Tyr Phe Pro Ile Lys Lys Pro Asn Asn Asn Lys Ile Leu Val Pro Lys
    50                  55                  60

Val Ser Gly Leu Gln Tyr Arg Val Phe Arg Ile His Leu Pro Asp Pro
65                  70                  75                  80

Asn Lys Phe Gly Phe Pro Asp Thr Ser Phe Tyr Asn Pro Asp Thr Gln
                85                  90                  95

Arg Leu Val Trp Ala Cys Val Gly Val Glu Val Gly Arg Gly Gln Pro
            100                 105                 110

Leu Gly Val Gly Ile Ser Gly His Pro Leu Leu Asn Lys Leu Asp Asp
        115                 120                 125

Thr Glu Asn Ala Ser Ala Tyr Ala Ala Asn Ala Gly Val Asp Asn Arg
    130                 135                 140

Glu Cys Ile Ser Met Asp Tyr Lys Gln Thr Gln Leu Cys Leu Ile Gly
145                 150                 155                 160

Cys Lys Pro Pro Ile Gly Glu His Trp Gly Lys Gly Ser Pro Cys Thr
                165                 170                 175

Asn Val Ala Val Asn Pro Gly Asp Cys Pro Pro Leu Glu Leu Ile Asn
            180                 185                 190

Thr Val Ile Gln Asp Gly Asp Met Val Asp Thr Gly Phe Gly Ala Met
        195                 200                 205

Asp Phe Thr Thr Leu Gln Ala Asn Lys Ser Glu Val Pro Leu Asp Ile
    210                 215                 220

Cys Thr Ser Ile Cys Lys Tyr Pro Asp Tyr Ile Lys Met Val Ser Glu
225                 230                 235                 240

Pro Tyr Gly Asp Ser Leu Phe Phe Tyr Leu Arg Arg Glu Gln Met Phe
                245                 250                 255

Val Arg His Leu Phe Asn Arg Ala Gly Ala Val Gly Glu Asn Val Pro
            260                 265                 270

Asp Asp Leu Tyr Ile Lys Gly Ser Gly Ser Thr Ala Asn Leu Ala Ser
        275                 280                 285

Ser Asn Tyr Phe Pro Thr Pro Ser Gly Ser Met Val Thr Ser Asp Ala
    290                 295                 300
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Gln Ile Phe Asn Lys Pro Tyr Trp Leu Gln Arg Ala Gln Gly His Asn
305                 310                 315                 320

Asn Gly Ile Cys Trp Gly Asn Gln Leu Phe Val Thr Val Val Asp Thr
                325                 330                 335

Thr Arg Ser Thr Asn Met Ser Leu Cys Ala Ala Ile Ser Thr Ser Glu
            340                 345                 350

Thr Thr Tyr Lys Asn Thr Asn Phe Lys Glu Tyr Leu Arg His Gly Glu
        355                 360                 365

Glu Tyr Asp Leu Gln Phe Ile Phe Gln Leu Cys Lys Ile Thr Leu Thr
    370                 375                 380

Ala Asp Val Met Thr Tyr Ile His Ser Met Asn Ser Thr Ile Leu Glu
385                 390                 395                 400

Asp Trp Asn Phe Gly Leu Gln Pro Pro Pro Gly Gly Thr Leu Glu Asp
                405                 410                 415

Thr Tyr Arg Phe Val Thr Ser Gln Ala Ile Ala Cys Gln Lys His Thr
            420                 425                 430

Pro Pro Ala Pro Lys Glu Asp Pro Leu Lys Lys Tyr Thr Phe Trp Glu
        435                 440                 445

Val Asn Leu Lys Glu Lys Phe Ser Ala Asp Leu Asp Gln Phe Pro Leu
    450                 455                 460

Gly Arg Lys Phe Leu Leu Gln Ala Gly Leu Lys Ala Lys Pro Lys Phe
465                 470                 475                 480

Thr Leu Gly Lys Arg Lys Ala Thr Pro Thr Thr Ser Ser Thr Ser Thr
                485                 490                 495

Thr Ala Lys Arg Lys Lys Arg Lys Leu
            500                 505
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 297 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..297

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
ATG CAT GGA GAT ACA CCT ACA TTG CAT GAA TAT ATG TTA GAT TTG CAA        48
Met His Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln
  1               5                  10                  15

CCA GAG ACA ACT GAT CTC TAC TGT TAT GAG CAA TTA AAT GAC AGC TCA        96
Pro Glu Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser
            20                  25                  30
```

```
GAG GAG GAG GAT GAA ATA GAT GGT CCA GCT GGA CAA GCA GAA CCG GAC      144
Glu Glu Glu Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp
         35                  40                  45

AGA GCC CAT TAC AAT ATT GTA ACC TTT TGT TGC AAG TGT GAC TCT ACG      192
Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys Asp Ser Thr
     50                  55                  60

CTT CGG TTG TGC GTA CAA AGC ACA CAC GTA GAC ATT CGT ACT TTG GAA      240
Leu Arg Leu Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu
 65                  70                  75                  80

GAC CTG TTA ATG GGC ACA CTA GGA ATT GTG TGC CCC ATC TGT TCT CAG      288
Asp Leu Leu Met Gly Thr Leu Gly Ile Val Cys Pro Ile Cys Ser Gln
                 85                  90                  95

AAA CCA TAA                                                          297
Lys Pro  *
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 98 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Met His Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln
 1               5                  10                  15

Pro Glu Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser
            20                  25                  30

Glu Glu Glu Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp
        35                  40                  45


Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys Asp Ser Thr
    50                  55                  60


Leu Arg Leu Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu
65                  70                  75                  80

Asp Leu Leu Met Gly Thr Leu Gly Ile Val Cys Pro Ile Cys Ser Gln
                85                  90                  95

Lys Pro  *
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CCCCGATATC GCCTTTAATG TATAAATCGT CTGG 34

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CCCCGATATC TCAAATTATT TTCCTACACC TAGTG 35

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

AAAGATATCT TGTAGTAAAA ATTTGCGTCC TAAAGGAAAC 40

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

AAAGATATCT AATCTACCTC TACAACTGCT AAACGCAAAA AACG 44

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AAAAGATATC ATGCATGGAG ATACACCTAC ATTGC 35

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTTTGATATC GGCTCTGTCC GGTTCTGCTT GTCC 34

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TTTTGATATC CTTGCAACAA AAGGTTACAA TATTGTAATG GGCC 44

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AAAAGATATC TGGTTTCTGA GAACAGATGG GGCAC 35

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TTTTGATATC GATTATGAGC AATTAAATGA CAGCTCAG 38

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TTTTGATATC GTCTACGTGT GTGCTTTGTA CGCAC 35

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TTTATCGATA TCGGTCCAGC TGGACAAGCA GAACCGGAC 39

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

TTTTGATATC GATGCCCATT ACAATATTGT AACCTTTTG 39

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 294 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..294

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
ATG AGT CTT CTA ACC GAG GTC GAA ACG CTT ACC AGA AAC GGA TGG GAG      48
Met Ser Leu Leu Thr Glu Val Glu Thr Leu Thr Arg Asn Gly Trp Glu
 1               5                  10                  15

TGC AAA TGC AGC GAT TCA AGT GAT CCT CTC ATT ATC GCA GCG AGT ATC      96
Cys Lys Cys Ser Asp Ser Ser Asp Pro Leu Ile Ile Ala Ala Ser Ile
            20                  25                  30

ATT GGG ATC TTG CAC TTG ATA TTG TGG ATT TTT TAT CGT CTT TTC TTC     144
Ile Gly Ile Leu His Leu Ile Leu Trp Ile Phe Tyr Arg Leu Phe Phe
        35                  40                  45

AAA TGC ATT TAT CGT CGC CTT AAA TAC GGT TTG AAA AGA GGG CCT TCT     192
Lys Cys Ile Tyr Arg Arg Leu Lys Tyr Gly Leu Lys Arg Gly Pro Ser
    50                  55                  60
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ACG GAA GGA GCG CCT GAG TCT ATG AGG GAA GAA TAT CGG CAG GAA CAG      240
Thr Glu Gly Ala Pro Glu Ser Met Arg Glu Glu Tyr Arg Gln Glu Gln
 65                  70                  75                  80

CAG AGT GCT GTG GAT GTT GAC GAT GTT CAT TTT GTC AAC ATA GAG CTG      288
Gln Ser Ala Val Asp Val Asp Asp Val His Phe Val Asn Ile Glu Leu
                85                  90                  95

GAG TAA                                                              294
Glu  *
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 97 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Met Ser Leu Leu Thr Glu Val Glu Thr Leu Thr Arg Asn Gly Trp Glu
 1               5                  10                  15

Cys Lys Cys Ser Asp Ser Ser Asp Pro Leu Ile Ile Ala Ala Ser Ile
            20                  25                  30

Ile Gly Ile Leu His Leu Ile Leu Trp Ile Phe Tyr Arg Leu Phe Phe
        35                  40                  45

Lys Cys Ile Tyr Arg Arg Leu Lys Tyr Gly Leu Lys Arg Gly Pro Ser
    50                  55                  60

Thr Glu Gly Ala Pro Glu Ser Met Arg Glu Glu Tyr Arg Gln Glu Gln
 65                  70                  75                  80

Gln Ser Ala Val Asp Val Asp Asp Val His Phe Val Asn Ile Glu Leu
                85                  90                  95

Glu  *
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
TTTTGATATC GATATGGAAT GGCTAAAGAC AAGACCAATC                          40
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TTTTGATATC GTTGTTTGGA TCCCCATTCC CATTG 35

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GTTATGACAT ACATACATTC TATG 24

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCATGCATTC CTGCTTGTAG TAAAAATTTG CGTCC 35

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CTACAAGCAG GAATGCATGG AGATACACC 29

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CATCTGAAGC TTAGTAATGG GCTCTGTCCG GTTCTG 36

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CATCTGAAGC TTATCAATAT TGTAATGGGC TCTGTCCG 38

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CATCTGAAGC TTACTTGCAA CAAAAGGTTA CAATATTGTA ATGGGCTCTG TCCG 54

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 69 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CATCTGAAGC TTAAAGCGTA GAGTCACACT TGCAACAAAA GGTTACAATA TTGTAATGGG 60

CTCTGTCCG 69

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CATCTGAAGC TTATTGTACG CACAACCGAA GCGTAGAGTC ACACTTG 47

WHAT IS CLAIMED IS:

1. A vaccine formulation comprising a human papilloma virus capsomere, said capsomere comprising a fusion protein comprising a human papilloma virus L1 protein adjacent amino acid residues from a second protein.

2. A vaccine formulation comprising a human papilloma virus capsomere, said capsomere comprising a truncated human papilloma virus L1 protein having a deletion of one or more amino acid residues necessary for formation of a virus-like particle.

3. The vaccine formulation of claim 2 wherein said capsomere comprises a fusion protein comprising a truncated human papilloma virus L1 protein adjacent amino acid residues from a second protein.

4. The vaccine formulation of any one of claims 1,2, or 3 wherein the L1 protein is encoded in the genome of a human papilloma virus selected from the group consisting of HPV6, HPV11, HPV16, HPV18, HPV33, HPV35, and HPV45.

5. The vaccine formulation of claim 4 wherein the papilloma virus is HVP16.

6. The vaccine formulation of any one of claims 2, 3, or 5 wherein carboxy terminal amino acid residues are deleted from the L1 protein.

7. The vaccine formulation of claim 6 wherein 1 to 34 carboxy terminal amino acid residues are deleted from the L1 protein.

8. The vaccine formulation of claim 7 wherein 34 carboxy terminal amino acid residues are deleted from the L1 protein.

9. The vaccine formulation of any one of claims 2, 3, or 5 wherein amino terminal amino acid residues are deleted from the L1 protein.

10. The vaccine formulation of any one of claims 2, 3, or 5 wherein internal amino acid residues are deleted from the L1 protein.

11. The vaccine formulation of claim 10 wherein the amino acid residues deleted from the L1 protein comprise a nuclear localization signal.

12. The vaccine formulation of claims 2 or 3 wherein the amino acids residues from the second protein are derived from an HPV protein.

13. The vaccine formulation of claim 12 wherein the HPV protein is an early HPV protein.

14. The vaccine formulation of claim 12 wherein the early HPV protein is selected from the group consisting of E1, E2, E3, E4, E5, E6, and E7.

15. A method of treating an individual infected with an HPV virus comprising the step of administering to a patient in need thereof an amount of the vaccine formulation of claims 1, 2, 3, 5, 7, 8, 11, 13 or 14 effective to reduce the level of HPV infection.

16. A method for preventing papilloma virus infection comprising the step of administering to an individual susceptible thereto an amount of the vaccine formulation of claims 1, 2, 3, 5, 7, 8, 11, 13 or 14 effective to inhibit HPV infection.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 98/20965

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/62 A61K39/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MÜLLER M ET AL.: "Chimeric papillomavirus-like particles" VIROLOGY, vol. 234, no. 1, 21 July 1997, pages 93-111, XP002091857 ORLANDO US see the whole document ---	1-8, 10-16
X	DE 44 35 907 A (GISSMANN L;ZHOU J; MÜLLER M) 11 April 1996 see the whole document ---	1-5, 10-16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 1999	16/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cupido, M

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 98/20965

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	LI M ET AL.: "Expression of the human papillomavirus type 11 L1 capsid protein in Escherichia coli" JOURNAL OF VIROLOGY, vol. 71, no. 4, April 1997, pages 2988-2995, XP002091858 AMERICAN SOCIETY FOR MICROBIOLOGY US see figure 7 ---	1-4,9
A	PAINTSIL J ET AL.: "Carboxy terminus of bovine pappilomavirus type-1 L1 protein is not required for capsid formation" VIROLOGY, vol. 223, no. 1, 1 September 1996, pages 238-244, XP002091859 ORLANDO US see figure 1 ---	1-16
A	ROSE R C ET AL: "SEROLOGICAL DIFFERENTIATION OF HUMAN PAPILLOMAVIRUS TYPES 11, 16 AND 18 USING RECOMBINANT VIRUS-LIKE PARTICLES" JOURNAL OF GENERAL VIROLOGY, vol. 75, no. 9, September 1904, pages 2445-2449, XP000604635 ---	1-16
A	WO 96 11274 A (US DEPARTMENT OF HEALTH) 18 April 1996 see examples 1-7 -----	1-16

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 98/20965

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15 and 16 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the vaccine formulation.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

..formation on patent family members

Inter· ·nal Application No
PCT/US 98/20965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4435907 A	11-04-1996	AU 4270196 A	02-05-1996
		CA 2202090 A	18-04-1996
		WO 9611272 A	18-04-1996
		EP 0809700 A	03-12-1997
WO 9611274 A	18-04-1996	US 5618536 A	08-04-1997
		AU 3828495 A	02-05-1996
		EP 0789766 A	20-08-1997
		JP 10506796 T	07-07-1998
		US 5855891 A	05-01-1999